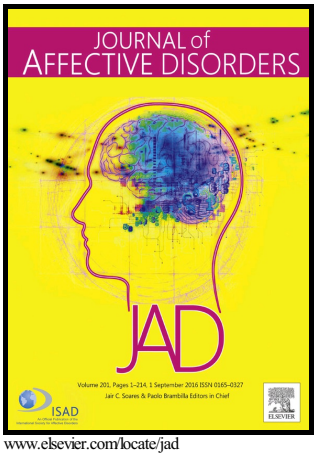

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White matter microstructure in boys with persistent depressive disorder

Veronika Vilgis[a,b,d*], Alasdair Vance[a,b], Ross Cunnington[c] and Timothy J. Silk[a]

[a]*Developmental Imaging, Murdoch Childrens Research Institute, Parkville, Australia*

[b]*Academic Child Psychiatry Unit, Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Parkville, Australia*

[c]*School of Psychology and Queensland Brain Institute, The University of Queensland, St Lucia, Australia*

[d] *UC Davis Center for Mind and Brain, Davis CA, USA*

[*]Correspondence to: UC Davis, Center for Mind and Brain, 267 Cousteau Place, Davis CA 95618. Tel.: +1 (530) 760-9478. vvilgis@ucdavis.edu

Abstract

Background

Persistent depressive symptoms in children and adolescents are considered a risk factor for the development of major depressive disorder (MDD) later in life. Previous research has shown alterations in white matter microstructure in paediatric MDD but discrepancies exist as to the specific tracts affected. The current study aimed to improve upon previous methodology and address the question whether previous findings of lower fractional anisotropy (FA) replicate in a sample of children with persistent depressive disorder characterised by mild but more chronic symptoms of depression.

Methods

White matter microstructure was examined in 25 boys with persistent depressive disorder and 25 typically developing children. Tract specific analysis implemented with the Diffusion Tensor Imaging - ToolKit (DTI-TK) was used to probe fractional anisotropy (FA) in eleven major white matter tracts.

Results

Clusters within the left uncinate, inferior fronto-occipital and cerebrospinal tracts showed lower FA in the clinical group. FA in the left uncinate showed a negative association with self-reported symptoms of depression.

Conclusions

The results demonstrate lower FA in several white matter tracts in children with persistent depressive disorder. These findings support the contention that early onset depression is associated with altered white matter microstructure, which may contribute to the maintenance and recurrence of symptoms.

Keywords: diffusion weighted imaging; MRI; white matter; fractional anisotropy; depression; children; pediatric

Introduction

Major depressive disorder (MDD) is one of the leading mental health problems in adults with an estimated worldwide lifetime prevalence of 11.2% (Kessler et al., 2015). Many cases of adult MDD begin in adolescence and risk factors for depression may occur even earlier (Kennard, Emslie, Mayes, & Hughes, 2006; Kovacs & Lopez-Duran, 2010). Adolescence is marked by continued changes in brain maturation and a rise in depressive symptoms during adolescence has often been associated with these changes (e.g., Davey, Yucel, & Allen, 2008; Foland-Ross et al., 2015; Schmaal et al., 2015).

Grey and white matter exhibit differential developmental patterns with the former showing an overall decrease and the latter an overall increase in volume from late childhood to early adulthood (Mills & Tamnes, 2014). While these measures focus on the macrostructure of the tissue, it is also possible to examine changes in the white matter microstructure using diffusion weighted imaging. White matter restricts the movement of water molecules, which is greater along the long axis of a fiber than across it. Common metrics used to describe these properties are fractional anisotropy (FA) and mean diffusivity (MD). In addition, axonal (AD) and radial diffusivity (RD) corresponding to movement along and across fibre bundles respectively can also be determined. FA is frequently reported in studies of white matter microstructure and lower FA is often interpreted as a reduction in myelination but it may equally correspond to differences in axon diameter, fiber bundle density, crossing fibers, myelin thickness or the cytoskeleton (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010; Jones, Knosche, & Turner, 2013; Winston, 2012).

Global white matter FA shows a gradual increase throughout childhood and adolescence with associated decreases in MD and RD (Mills & Tamnes, 2014). However, regional differences have been observed with fibres connecting frontal and temporal cortices (Colby, Van Horn, & Sowell, 2011; Lebel & Beaulieu, 2011; Tamnes et al., 2010) including the cingulum and uncinate fasciculi, which develop at a slower rate than some of the other fibres (Lebel et al., 2012; Olson, Von Der Heide, Alm, & Vyas, 2015; Westlye et al., 2010). Environmental stressor or genetic predisposition may differentially affect the development of white matter pathways and concomitant changes may relate to the development of depressive symptoms

(Ladouceur, Peper, Crone, & Dahl, 2012).

To date there have been only few investigations into white matter microstructure in pediatric depressive disorders and there is little consistency across results. Tracts that have been reported by more than two studies include the cingulum, the uncinate fasciuli and the inferior fronto-occipital fasciculi (Aghajani et al., 2013; Bessette, Nave, Caprihan, & Stevens, 2014; Cullen et al., 2010; Henderson et al., 2013; LeWinn et al., 2014). Changes in the microstructure of the corpus callosum have also been reported by several studies but vary in the exact location with differences reported in the genu (Bessette et al., 2014; LeWinn et al., 2014) as well as the body (Aghajani et al., 2013; Bessette et al., 2014; LeWinn et al., 2014). Generally, lower FA is observed in these fibre bundles in the clinical group but increased FA has also been reported (Aghajani et al., 2013; Henderson et al., 2013). In addition to the above findings, a whole range of other fibre bundles have been reported by individual studies that have not yet been replicated (e.g., Bessette et al., 2014).

In a review of structural and functional neuroimaging studies of pediatric MDD, Hulvershorn et al. (2011) propose that at least some of the alterations in brain structure and function may predate psychopathology. Support comes from a study that examined a group of adolescents with a parental history of depression that reported lower FA in the left cingulum, the splenium of the corpus callosum, the uncinate, superior longitudinal and inferior fronto-occipital fasciculi (Huang, Fan, Williamson, & Rao, 2011). However, the study only included a small sample size (18 high-risk youth and 13 controls) and has not yet been replicated. While Huang et al. (2011) did not find correlations with symptoms, other studies have found associations between FA in the uncinate and trait anxiety in healthy individuals (Kim & Whalen, 2009;

Montag, Reuter, Weber, Markett, & Schoene-Bake, 2012); thus it is not clear whether lower FA precedes symptom onset or simply reflects symptom severity. Although the function of the uncinate is still largely unknown several previous studies have implicated its role in reversal learning, reward processing and long-term memory retrieval (Olson et al., 2015). The latter two are often impaired in MDD suggesting that white matter microstructure in the uncinate may be altered.

Beyond the uncinate Henderson et al. (2013) showed that irritability was associated with lower FA in the sagittal striatum, anterior corona radiata, and tracts leading to prefrontal and temporal cortices while anhedonic symptoms were associated with structural alterations in the anterior limb of the internal capsule and projection fibers to the orbitofrontal cortex. White matter associations with other symptoms that often coexist with depressive disorders such as low self-esteem, hopelessness and attention difficulties have not been examined in children and adolescents with depressive disorders.

Most investigations thus far have employed the tract based spatial statistics (TBSS) procedure (Smith et al., 2006) that projects volumetric data onto a white matter skeleton. While this has advantages to other methods such as voxel-based morphometry, TBSS has limited anatomical specificity and fails to take into account orientation information in the diffusion data (Bach et al., 2014). In addition, previous methods most commonly report values averaged across tracts and do not provide location specific information within tracts. A recent study has shown that there is considerable variation within tracts as they mature (Chen, Zhang, Yushkevich, Liu, & Beaulieu, 2016). To improve upon previous shortcomings the current study used full tensor information for improved registration and employed tract specific analysis to

localize any white matter differences within tracts. Our aim was to investigate white matter microstructural differences between a sample of boys with persistent depressive disorder and matched typically developing children. Studying a group of children characterized by chronic but mild symptoms may contribute to a better understanding of whether persistency of symptoms may impact on brain structure to a greater degree than severity of symptoms. In addition, these children are at increased risk of developing a major depressive episode (Klein, Schwartz, Rose, & Leader, 2000) and information about underlying neurobiology may help in identifying risk factors that may potentially be the target of early interventions. In line with previous findings in pediatric depression we expected lower FA in white matter fibre tracts in the clinical group, particularly the uncinate fasciculi and the inferior-fronto-occipital fasiculi. We also predicted to find an association between depressive symptoms and FA in the left uncinate fasciculus.

Method

Participants

A total of 50 male young people aged nine to sixteen years participated in this study. 25 met DSM-V diagnostic criteria for persistent depressive disorder (DSM-IV dysthymic disorder) and were recruited from a pediatric psychiatric outpatient clinic at The Royal Children's Hospital, Melbourne, Australia. Our previous study using functional magnetic resonance imaging (fMRI) (Vilgis, Chen, Silk, Cunnington, & Vance, 2014) included 10 of the 25 patients with DD and 10 of the 25 typically developing children. Diagnoses were assessed categorically using the Anxiety Disorders Interview Schedule (ADIS) (parent and child version) (Silverman & Albano, 1996) and dimensionally with the Child Behavior Checklist (CBCL)

(Achenbach & Edelbrock, 1983). Young people also completed the Children's Depression Inventory (CDI) (Kovacs, 1992). Of the 25 boys that met diagnostic criteria for persistent depressive disorder thirteen also met criteria for generalized anxiety disorder, nine for separation anxiety disorder and seven for social phobia as rated by their caregiver on the ADIS. Eleven also met diagnostic criteria for oppositional defiant disorder (ODD) and five for conduct disorder (CD). Persistent depressive disorder can be diagnosed based on primarily irritable mood, which has been shown to contribute to greater disruptive behavior disorder symptoms (Harrington, Fudge, Rutter, Pickles, & Hill, 2001). Therefore, a diagnosis of comorbid CD and/or ODD was allowed for inclusion in the current study. Furthermore, the clinical presentations of 'pure' and comorbid depressive and conduct disorders have been found to be very similar unlike comorbid Attention-deficit/hyperactivity disorder (ADHD) and depression (Angold, Costello, & Erkanli, 1999; Ezpeleta, Domenech, & Angold, 2006). Hence, a diagnosis of ADHD was an exclusion criterion for the current study. Typically developing children (TD) were recruited from local schools and matched for age to the clinical group. They completed the same semi-structured clinical interviews and questionnaires as the clinical participants. Participants were included if they were male, right-handed as assessed using a subtest of the Scored Developmental Neurological Examination (Taylor, Everitt, et al., 1986; Taylor, Schachar, Thorley, & Wieselberg, 1986) and with a full-scale IQ above 70 as assessed by the Wechsler Intelligence Scale for Children (WISC-IV). Maternal education was measured with the Parental Account of Childhood Symptoms (PACS) (Taylor et al., 1986). Exclusion criteria were the presence of an intellectual disability, learning disorder or known neurological or endocrine condition. Participants were also excluded if they had a previous diagnosis

for an Autistic Spectrum Disorder, Bipolar Disorder or Psychotic Disorders. All participants were medication-naïve except for one clinical participant who was treated with fluoxetine. The study was approved by The Royal Children's Hospital Human Research Ethics Committee and all participants and their parents provided written informed consent. Table 1 lists demographic and clinical variables for both groups.

Image Acquisition

Data were acquired on a 3-Tesla Siemens Tim Trio MRI scanner (Siemens, Erlangen, Germany), at The Royal Children's Hospital Melbourne. Diffusion-weighted echoplanar images (EPI) for 30 children (15 clinical matched to 15 TD on age) were acquired along 30 diffusion gradient directions for acquisition of 58 axial slices through the whole brain with in-plane resolution of 2.30 × 2.30 mm (b value of 1000 s/mm^2, TR = 7293 ms, TE = 87 ms, 90° flip angle, number of averages = 1, matrix size = 98 × 98, slice thickness = 2.3 mm, spacing between slices = 2.3 mm). Diffusion-weighted EPI of the remaining 20 children (10 clinical matched to 10 TD on age) were acquired on the same scanner along 30 diffusion gradient directions for acquisition of 40 axial slices with in-plane resolution of 1.72 × 1.72 mm (b value of 1000 s/mm2, TR = 5200 ms, TE = 88 ms, 90° flip angle, number of averages = 1, matrix size 128 x 128, slice thickness = 3.0 mm, spacing between slices = 3.0 mm). To account for any potential differences between the groups due to scanning sequence scan was entered as a covariate of no interest in all analyses.

Data Analysis

Preprocessing was conducted using FSL (Oxford, UK) FMRIB's Diffusion Toolbox (FDT). Eddy current correction was done using eddy_correct to correct for gradient-

coil distortions and small head motions, using affine registration to a reference volume. Maps of FA, MD, and the primary, secondary, and tertiary eigenvalues were calculated from the diffusion-weighted images using DTI- Fit, which fits a diffusion tensor model to each voxel, estimating the principle directions of diffusion. Data was then transformed to use within DTI-TK software (v 2.3.1) (Zhang et al., 2007; Zhang, Yushkevich, Alexander, & Gee, 2006) using the fsl_to_dtitk command. DTI-TK is currently recognized as one of the best available tools for registering dti data (Wang et al., 2011). It takes into account the directional information of the diffusion tensors, which is used to align all subjects' data through rigid, affine, and nonlinear registration steps. Before registration, all data were visually inspected and checked for outliers. Each participant's data was first registered and spatially normalized using a template created from a random subsample (8 participants matched for scan type and control-patient ratio). Tensor volumes were resampled to a voxel space of 128 × 128 × 64 with voxel dimensions equal to 1.72 × 1.72 × 2.5 mm^3. Following initial rigid, affine and diffeomorphic registration the resulting group template was registered to the default adult template recommended for tract specific analysis in DTI-TK. The combined affine and diffeomorphic transformations from both the registration of the individual image to the group specific sample and the registration of the group specific sample to the adult template were used to bring individual images into standard space.

Tract-specific analysis (TSA) (Yushkevich, Zhang, Simon, & Gee, 2008; Zhang et al., 2010) allows computing white matter tract-specific attributes such as FA, ADC (apparent diffusion coefficient, a scalar measurement of overall diffusivity equal to MD), RD and AD across the whole population. In this study, the tensor averaging dimensionality reduction strategy was adopted. Results are projected onto a medial

model, a sheet-like structure that represents a 3D tract. Eleven major white matter tracts were investigated: the corpus callosum (CC), the corticospinal tracts (CST), inferior fronto-occipital tracts (IFO), inferior longitudinal tracts (ILF), superior longitudinal tracts (SLF), and uncinates (UNC). These eleven major tracts are suited to the sheet-like analysis unlike tracts that are tube-based (e.g., the cingulum) and therefore excluded from the analysis. To determine individual clusters within each tract permutation-based non-parametric suprathreshold cluster analysis was performed. 10000 random permutations were performed with a cluster threshold of $p < 0.001$ (uncorrected) and a family-wise error rate corrected cluster significance of $p < 0.05$. Demographic, clinical and head motion data was analyzed using independent samples t-tests and a Wilcoxon-Mann-Whitney test to examine group differences in maternal education using SPSS (v 21).

Results

Groups did not differ in age but significant differences in IQ and depressive symptoms were found. No significant differences between the underlying distributions in maternal education were found between the two groups. There were also no significant differences in absolute and relative head motion between the clinical and control group (Table 1).

Between group analysis

TSA revealed several significant clusters with lower FA values in the clinical as compared to the typically developing group. Significant clusters were found in left

CST, left IFO and left UNC. No differences in MD, RD and AD were found in these tracts.

Symptom Correlations

Based on previous work which suggests a relationship between negative emotionality (Montag et al., 2012) and the left UNC we regressed the clinical participants' CBCL-anx/dep scores and CDI scores onto mean FA for this tract adjusting for scan. A significant negative relationship between CDI scores and FA was found (Std β = -0.427; t = -2.229; p = 0.036) but not for CBCL scores (Std β = 0.309; t = 1.519; p = 0.143). Exploratory post hoc analysis examining symptom associations with the left CST and left IFO revealed a significant positive association between anxious/depressed symptoms and the left CST (Std β = 0.473; t = 2.966; p = 0.007) and a trend for a negative association between mean FA of the left IFO and CDI scores (Std β = - 0.327; t = -2.076; p = 0.050). None of the other symptom FA associations were significant for these two tracts.

Discussion

This study aimed to address the question whether white matter microstructural properties differ in young people with persistent depressive disorder compared to typically developing children. Because several previous studies in paediatric depression have shown alterations in FA in the UNC and IFO we hypothesized that these tracts would show lower FA in the present sample. We found clusters in both the UNC and IFO that exhibited lower FA in the clinical compared to the TD group. Differences were found in left lateralized tracts only. In addition, a cluster within the

left CST also showed lower FA in the clinical as compared to the TD group. Self-reported depressive symptoms were associated with less FA in the left UNC in the clinical group.

The left UNC has been identified in several previous white matter microstructure analyses in pediatric depression (Aghajani et al., 2013; Bessette et al., 2014; Cullen et al., 2010; LeWinn et al., 2014) and symptom associations were found between FA in this tract and trait anxiety (Montag et al., 2012). Here, a negative relationship was found between children's self-reported depressive symptoms and FA. The UNC is the main tract connecting the prefrontal cortex with limbic structures including the amygdala and hippocampus (Catani, Howard, Pajevic, & Jones, 2002) and is thought to support emotion regulation, reversal learning, long-term memory retrieval and reward processing (Olson et al., 2015). All of these have been found to function atypically in patients with MDD (e.g. Dickstein et al., 2010; Forbes et al., 2006; Hammar & Ardal, 2009; Kovacs, Joormann, & Gotlib, 2008) but may not be unique to the disorder. There is increasing evidence that depression onset during childhood and/or adolescence is associated with alterations in brain structure (Schmaal et al., 2015), greater relapse risk and continuity into adulthood (Garber & Rao, 2014). Given its prolonged maturational trajectory, the UNC may be particularly vulnerable to stressors that have the potential to alter the normal developmental trajectory and contribute to the onset and maintenance of psychopathology.

The left IFO connects occipital, temporal and superior parietal regions to the frontal lobe. Its function is still being investigated but evidence suggests a supportive role in processing attentional, semantic language and visual information (Sarubbo, De Benedictis, Maldonado, Basso, & Duffau, 2013). Lesion studies have shown that

damage to the IFO impairs the recognition of facial affect (Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009). Given that depression has been associated with a negative attentional processing bias (Jacobs, Reinecke, Gollan, & Kane, 2008; Vilgis, Silk, & Vance, 2015), it is likely that alterations in white matter microstructure of the IFO relate to alterations in facial affect processing. Three other studies have reported reduced FA in the IFO in paediatric MDD (Bessette et al., 2014; Cullen et al., 2010; LeWinn et al., 2014) as well as in a sample of adolescents at-risk for depression (Huang et al., 2011). However, no study to date has directly tested whether white matter metrics relate to attention bias scores in individuals with depressive disorders.

Results also revealed reduced FA in a cluster within the left CST. Although we did not hypothesize alterations in this tract, two previous studies have shown reductions in FA in this tract in adolescents and children with MDD (Bessette et al., 2014; LeWinn et al., 2014). The CST plays a role in the processing of sensorimotor information and coordination. It runs through the internal capsule, which projects information past the basal ganglia and separates the thalamus from the putamen, globus pallidus and the caudate nucleus. Alterations in this tract may relate to motor retardation and slowed reaction times often seen in MDD. Exploratory post-hoc analysis also revealed a positive association between FA for the entire CST and parent reported anxious-depressive symptoms in the clinical group. While these results need to be interpreted with caution due to the exploratory nature, one possible explanation for the positive association may be that there are regional variations within the tract that show contribute to overall greater FA in the clinical group compared to the TD group (Chen et al., 2016). As we did not test for greater FA across tract in the clinical

group future studies will have to replicate this finding in a larger sample.

The generalizability of our findings is limited by our small sample, which included only male participants and spanned a wide age range. Increasingly, the role of pubertal hormones is recognized as playing an important part in white matter maturation (Ladouceur et al., 2012) and may contribute to the emergence of sex differences in the prevalence of depression throughout adolescence. Future studies should include endocrine measures when examining developmental samples that spread across different pubertal stages and consider sex differences. A proportion of the clinical sample had comorbid conditions and we cannot rule out that comorbid symptoms drove differences in white matter structure between the groups. However, the co-occurrence of anxiety disorders and disruptive behavior disorders with depression is common (Angold et al., 1999). Therefore, our sample can be considered representative of the majority of young male individuals with persistent depressive disorder. Several previous studies have shown altered white matter microstructure in children exposed to early life stressors (Huang, Gundapuneedi, & Rao, 2012) and children with a familial history of affective disorders (Huang et al., 2011). Future studies may improve upon the current sample by taking previous life history and familial psychopathology into account. IQ differences between the two groups may account for some of the observed results; however, IQ scores of the clinical participants may not have been representative of each individual's true ability given reduced motivation, increased anxiety and/or increased concentration difficulties known to often accompany depressive disorders. A strength of the current study is the improved registration by using tensor direction information. However, analysis was concentrated on tracts that exhibit sheet-like structure excluding tube-like tracts such as, for example, the fornix and cingulum. DTI-TK's tract-specific analysis currently

does not provide adequate means to examine these tube-like tracts, therefore future work may extend the current findings by drawing upon geometrical models for tube-like structures as developed by others (Colby et al., 2012; Jones, Travis, Eden, Pierpaoli, & Basser, 2005).

In conclusion, the present study found reduced FA in the left UNC, IFO and CST in a group of boys with persistent depressive disorder. The present results suggest that mild but chronic depressive symptoms in late childhood and adolescence are associated with alterations in white matter tracts. Future studies should address the question of whether white matter alterations precede or are a result of depression onset and how these shape the trajectory of affected individuals.

Disclosure

Conflict of Interest:

All authors declare that they have no conflicts of interest.

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Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Contributors

Authors AV, RC and TS designed the study and wrote the protocol. Author AV oversaw the clinical assessment of participants and confirmed diagnosis. Author TS contributed to the MRI data collection and oversaw analysis and interretation of the imaging data. Author VV managed the literature searches and analyses. Authors VV undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Figure 1: The medial models of the left UNC, left CST and left IFO in three dimensions are colored by the t-score for the hypothesis FA(TD) > FA(persistent depressive disorder). Statistically significant clusters are marked by a white outline.

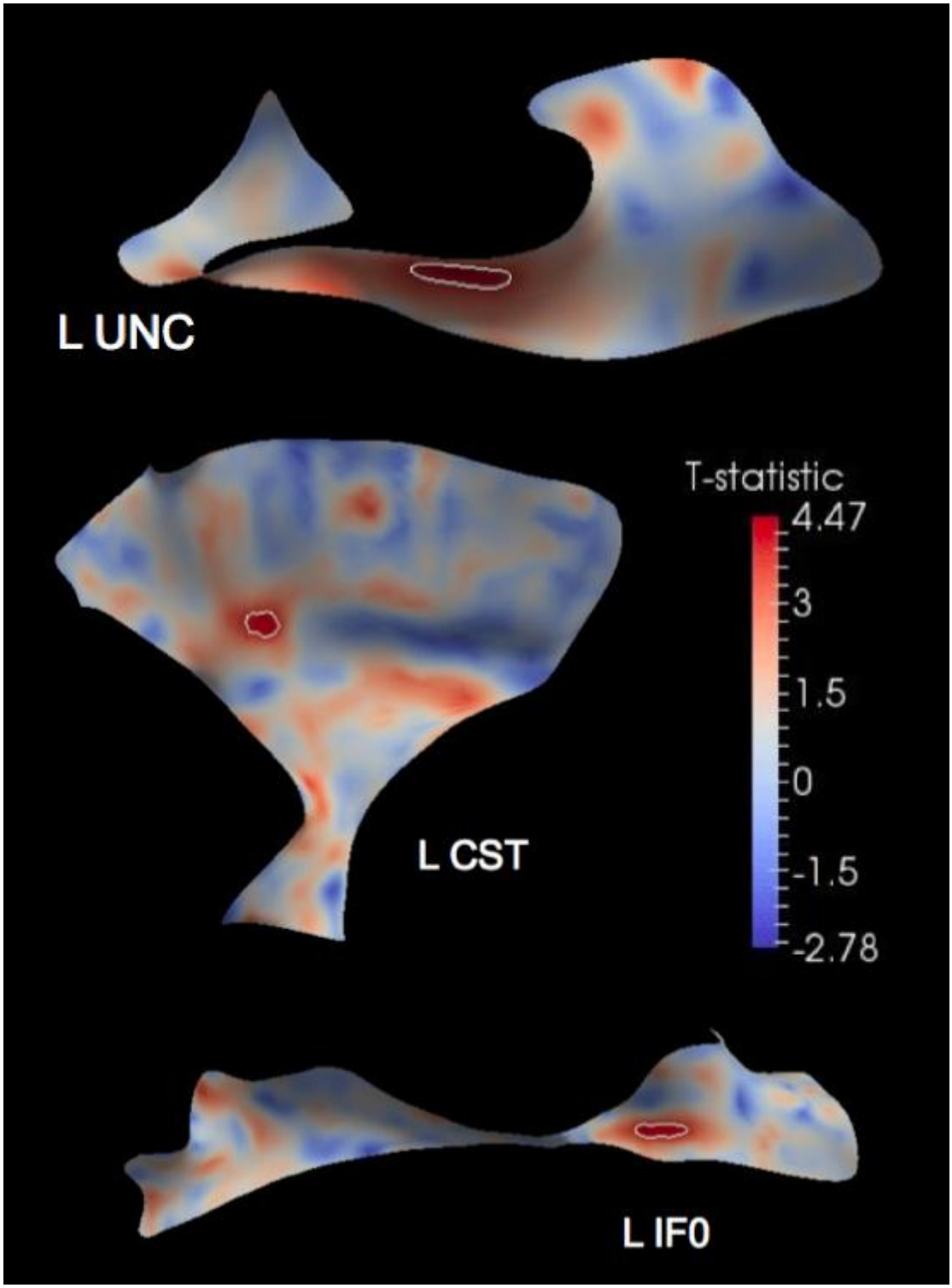

Table 1: Demographic, clinical and head motion information

	PDD (N=25)		TD (N=25)			
	M.	**S.D.**	**M.**	**S.D.**	**t (df)**	**p**

Age	12.1	1.8	11.9	2.0	-0.360 (48)	.720
Full Scale IQ	90.1	11.4	107.2	8.9	5.889 (48)	< .001
CBCL – Anxious/Depressed Scale Parent Rating	70.2	11.8	52.8	4.6	-6.891 (31.1)*	< .001
CDI self report	57.0	13.9	41.3	4.3	-5.403 (28.6)*	< .001
Relative Head Displacement (mm)	0.67	0.21	0.57	0.13	1.949 (48)	.057
Absolute Head Displacement (mm)	1.57	0.69	1.53	0.55	0.269 (48)	.789
	Med.		**Med.**		**U**	**p**
Maternal Education	6.00		6.00		228.500	.134

CBCL=Child Behavior Checklist, CDI=Children's Depression Inventory, M.=Mean, S.D.= Standard Deviation, Med.=Median
**Equal variance not assumed; adjusted degrees of freedom (df) are reported*

Table 2: Statistically significant clusters in three tracts showing less FA in the clinical compared to the control group.

Fasciculus	**Metric**	**Area mm^2**	**t**	**p corr**
Left IFO	FA	49.5	3.364	0.015
Left UNC	FA	34.6	3.354	0.005
Left CST	FA	43.7	3.349	0.022

FA = fractional anisotropy

Highlights

- White matter alterations found in specific tracts in boys with persistent depressive disorder
- Boys with depression exhibited lower FA in uncinate, inferior fronto-occipital and cerebrospinal tracts
- White matter in left uncinate associated with self-reported symptoms of depression.
- Alterations in white matter may contribute to maintenance and recurrence of depressive symptoms in children